## Title

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# Cartilage Morphology and $T_{1\rho}$ and $T_2$ Quantification in ACL-reconstructed Knees: A 2-year Follow-up

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## Abstract

**Objective—**To describe cartilage matrix and morphology changes, assessed using quantitative MRI, after acute anterior cruciate ligament (ACL) injury relative to controls and longitudinally during 2 years following reconstruction.

**Method—**Fifteen patients with acute ACL injuries and sixteen healthy volunteers with a similar demographic profile but no history of osteoarthritis or knee injury were studied. The injured knee of each participant was imaged with a 3.0 T MR scanner at baseline (prior to ACL reconstruction); patients' knees were re-imaged 1- and 2-years after ACL reconstruction. Cartilage $T_{1\rho}$ and $T_2$ values in full thickness, superficial layers, and deep layers, and cartilage thickness of the full layer were quantified within subcompartments of the knee joint.



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**Conflict of Interest**
The authors have no conflict of interest to disclose with regard to the subject matter of this present manuscript.

**Authors' Contributions**
All authors approved the final version of the manuscript.
Favian Su: data collection, analysis, and interpretation; drafting and critically revised the article.
Joan F. Hilton: statistical data analysis; critically revised the article for intellectual content.
Lorenzo Nardo: data analysis and interpretation; critically revised the article for intellectual content.
Samuel Wu: data collection and processing; provided technical support.
Fei Liang: data collection and processing; provided technical support.
Thomas M. Link: data analysis and interpretation; critically revised the article for intellectual content.
C. Benjamin Ma: conception and design of the study, patient recruitment, and management; provided clinical input.
Xiaojuan Li: conception and design of the study, data analysis and interpretation; drafting and critically revised the article for intellectual content.

**Results—**In the posterolateraltibial cartilage, $T_{1\rho}$ values were significantly higher in ACL-injured knees than control knees at baseline and were not fully recovered at the 2-year after ACL reconstruction. $T_{1\rho}$ values of medial tibiofemoral cartilage in ACL-injured knees increased over the 2-year study and were significantly elevated compared to that of the control knees. $T_2$ values in cartilage of the central aspect of the medial femoral condyle at the 2-year follow-up were significantly elevated compared with control knees. Cartilage in the posterior regions of the lateral tibia was significantly thinner, while cartilage in the central aspect of the medial femur was significantly thicker than that of controls. Patients with lesions in the posterior horn of the medial meniscus exhibited significantly higher $T_{1\rho}$ values in weight-bearing regions of the tibiofemoral cartilage than that of control subjects over the two year period, whereas patients without medial meniscal tears did not.

**Conclusion—**Quantitative MRI provides powerful *in vivo* tools to quantitatively evaluate early changes of cartilage matrix and morphology after acute ACL injury and reconstruction, which may possibly relate to the development of post-traumatic osteoarthritis in such joints.

### Keywords

Anterior cruciate ligament; Post-traumatic osteoarthritis; Magnetic resonance imaging; $T_{1\rho}$; $T_2$; Cartilage

## Introduction

Anterior cruciate ligament (ACL) rupture is a common and serious knee injury. ACL-injured knees are currently treated by reconstructing the ligament with biological tissue grafts, and this surgical procedure has been shown to improve the stability and function of the knee in most patients[1]. However at 5 to 15 years after surgery, radiographic studies document that approximately 50% of patients who have undergone ACL reconstruction are susceptible to post-traumatic osteoarthritis (OA)[2–6]. In many young individuals, this injury leads to the development of OA with knee-related symptoms that severely affects their quality of life[7,8].

Standard magnetic resonance imaging (MRI) techniques, which include fat-saturated $T_2$-weighted, proton density-weighted fast spin echo (FSE) and $T_1$-weighted spoiled gradient echo (SPGR) sequences, have been found to be useful in detecting morphological changes associated with cartilage breakdown noninvasively[9]. These sequences, however, are limited from detecting early degenerative changes of the cartilage matrix[10,11]. Recent developments in MRI techniques, such as $T_{1\rho}$, $T_2$, and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), can be used to quantify the biochemical changes in cartilage matrix and detect early cartilage degeneration[12–19]. A few previous studies applied $T_{1\rho}$, $T_2$, and dGEMRIC imaging to detect cartilage matrix composition changes after ACL injury and reconstruction[20–24].

Our group previously reported that $T_{1\rho}$ quantification was able to detect persistent damage in the lateral tibial cartilage and early degeneration in the medial tibiofemoral cartilage of ACL-injured knees 1 year after reconstruction[21]. Consistent with previous clinical studies, our study also reported that patients with medial meniscal injury had a higher $T_{1\rho}$ increase than those without, which suggests that meniscal injury is a potential risk factor for post-traumatic OA development[3–5].

Despite promising results, the 1-year study warranted a longer follow-up to better understand changes that were observed. Thus, the objectives of the present study are to 1) quantify longitudinal changes in cartilage morphology and matrix in ACL-injured knees two years after ACL reconstruction using quantitative MRI (thickness, $T_{1\rho}$, and $T_2$ quantification); and 2) identify baseline MR measures that predict cartilage morphology and

matrix $T_{1\rho}$ and $T_2$ progression at 2-year. We hypothesize that 1) early degeneration of the lateral and medial tibiofemoral cartilage of ACL-injured knees will persist two years after reconstruction and that 2) baseline meniscal injury and bone marrow edema-like lesions (BMEL) may predict cartilage degeneration progression two years after reconstruction.

## Materials and Methods

### Subjects

The study was approved by the Committee for Human Research at our institution and all subjects gave informed consent. Sixteen healthy controls and fifteen patients with clinically diagnosed acute ACL rupture were studied. The exclusion criteria included knee radiograph Kellgren-Lawrence (KL) score > 0 for controls and KL score > 2 for patients, prior diagnosed inflammatory arthritis, or previous injury on either knee. Patients who required surgical intervention for other injuries, including collateral ligament and posterior cruciate ligament tears, were excluded from the study. All patients underwent ACL reconstruction (all but one were performed by (C.B.M.), an experienced orthopedic surgeon). One patient underwent concomitant lateral meniscal repair, two patients underwent medial meniscectomy, and one underwent debridement of the posterior lateral horn.

### Imaging Protocols

Knee radiography was performed after injury but prior to ACL reconstruction (baseline). The standard knee radiographic protocol included bilateral semiflexed weight-bearing view, 30° flexion lateral view, and bilateral patellofemoral sunrise view. All MR examinations were acquired using a 3 T GE Signa MR scanner (HDx, General Electric Healthcare, Milwaukee, WI) with a transmit/receive quadrature knee coil (Clinical MR Solutions, Brookfield, WI). MR images were taken at baseline (n = 15) and at 1 (n = 15) and 2 (n = 12) years after surgery. Controls were imaged at baseline only. Table 1 summarizes the clinical, $T_{1\rho}$, and $T_2$ quantification sequences previously developed by our lab[21].

### Conventional Radiographic and Clinical Diagnostic MR Assessment

All radiographs and clinical MR images were reviewed by two experienced musculoskeletal radiologists (L.N. and T.M.L.). The radiographic findings were scored according to the Kellgren-Lawrence scale[25]. The MR images were analyzed for meniscal lesion, effusion, and cartilage lesion by using modified subscores of the Whole-Organ Magnetic Resonance Imaging Score system, Table 2[26].

### Quantification of Bone Marrow Edema-like Lesions

In all subjects, BMELs were defined as focal subchondral high signal intensity lesions on $T_2$-weighted fat-saturated FSE images. BMELs were segmented semi-automatically using a threshold developed previously by our lab[27]. The final regions based on the threshold were verified by a radiologist (L.N.).

### Cartilage Thickness and MR Relaxation Time Quantification

Cartilage was segmented semi-automatically on sagittal SPGR images by using a in-house program[28]. The LFC, MFC, LT, and MT were further divided into subcompartments with regard to the meniscus as shown in our 1-year report[21]. An iterative minimization process was used to calculate the thickness of each subcompartment.

The $T_{1\rho}$ and $T_2$ maps were reconstructed by fitting the images pixel by pixel to the following equations: $S(TSL) \propto S_0 \exp(-TSL/T_{1\rho})$ for $T_{1\rho}$ and $S(TE) \propto S_0 \exp(-TE/T_2)$ for $T_2$, where TSL is the time of spin lock, TE is the echo time, and S is the signal intensity. The

signal-to-noise ratio for each subcompartment in images with TSL = 80 ms or TE = 45.6 ms ranged from 6.8 to 14.8, which is sufficient for robust $T_{1\rho}$ and $T_2$ quantification.

$T_{1\rho}$ and $T_2$ maps were registered to SPGR images, and cartilage contours generated from the SPGR images were overlaid onto the registered $T_{1\rho}$ and $T_2$ maps. To reduce artifacts caused by partial volume effects with synovial fluid, relaxation times greater than 150 ms on $T_{1\rho}$ and relaxation times greater than 100 ms on $T_2$ were automatically removed from quantification. In addition, $T_{1\rho}$ and $T_2$ values were quantified for two equally spaced layers, the deep and the superficial, by using an in-house program[29].

### Statistical Analysis

Restricted maximum-likelihood mixed-effects regression models were used to analyze outcomes that were measured at multiple times and/or locations within individuals. Subjects are modeled as random effects via variance components correlation matrix to ensure that standard error estimates account for correlated outcomes within subjects. To allow close estimation of effects while avoiding over-fitting, the models include two-way interactions among fixed-effect covariates.

Among all subjects, cartilage thickness was modeled as a function of *Bone* (femur, tibia, or patella), *Side* (lateral or medial), *Group* (controls vs patients), and *Year* (baseline, 1-year, or 2-year, 2 degrees of freedom (DF)), adjusted for subcompartment and baseline $T_{1\rho}$. Among patients, linear regression was used to estimate associations of baseline BMEL volume with bone, age, sex, and BMI. BMEL volumes at each time point were compared using rank tests. Also among patients, we modeled the longitudinal pattern in $T_{1\rho}$ and $T_2$ to determine if they vary significantly as a function of clinical (presence of baseline meniscal injury, and baseline BMEL volume) and demographic characteristics (age, sex, BMI) and if any of the latter should be included in the primary analyses.

We separately modeled $T_{1\rho}$ and $T_2$ as functions of *Group*, *Year*, *Bone*, *Side*, *Layer* (superficial or deep), and *Subcompartment* (femur included 4–5 (4 DF) and tibia included 3 (2 DF) per side, whereas patella had no side or subcompartments). We further modeled $T_{1\rho}$ and $T_2$ as functions of *Group* and *Year* in models stratified by bone, side, and layer.

In post-hoc analysis, Wilcoxon signed-rank tests were employed to compare the $T_{1\rho}$ and $T_2$ of all subcompartments between the patients and controls. A Spearman rank correlation was performed between mean $T_{1\rho}$ and $T_2$ values of different subcompartments. Data were reported as mean (SD) unless otherwise noted as mean (SE) in the results.

## Results

### Clinical Profiles

Control and patient groups were similar in age, gender, and BMI (Table 3(a)). The mean time from injury to baseline MRI was 46.1 days and from injury to ACL reconstruction was 83.1 days.

Based on radiographs, 12 patients had KL score = 0, two had KL = 1 and one had KL = 2. On the basis of MR images, all ACL-injured knees exhibited effusion (grade 1 (n = 5), grade 2 (n = 9), grade 3 (n = 1)).

Ten patients had a mensical lesion involving either the posterior horn of the medial or the lateral meniscus: 3 had isolated medial tears, 3 had isolated lateral tears, and 4 had both medial and lateral meniscal tears, Table 3(b). At baseline, 2 patients had no cartilage lesions, 5 had one, and 8 had more than one. At the 1-year follow-up, all 15 patients had a lesion in

at least one compartment with 31 cartilage lesions being observed: 7 in the patella, 6 in MFC, 6 in LFC, 1 in MT and 11 in LT. In the 12 ACL-injured patients who had 2-year scans, 23 cartilage lesions were observed: 6 in the patella, 4 in MFC, 5 in LFC, and 8 in LT.

### Quantification of Bone Marrow Edema-like Lesions

At baseline, all 15 patients had a BMEL in at least one compartment. No significant effect of age, sex, or BMI on baseline BMEL volume was found. The LT was most affected and had the largest mean volume (n = 14; 5.79 (4.4) $cm^3$), followed by the LFC (n = 9; 3.64 (4.1) $cm^3$), MT (n = 9; 1.32 (1.2) $cm^3$), and the MFC (n = 5; 1.61 (1.5) $cm^3$).

BMEL volumes decreased significantly at 1-year and 2-year follow-ups compared to baseline ($p < 0.001$). At 1-year, 11 patients had a BMEL in at least one compartment (volume: 0.42 (0.5) $cm^3$), with three patients developing new lesions in the LFC (n = 1) or MFC (n = 2). In the second year, four patients had a BMEL in one compartment (0.24 (0.1) $cm^3$), with one patient developing a new lesion in the LFC.

### Cartilage Thickness

The estimated mean cartilage thickness did not differ significantly between patients and controls ($p = 0.31$). The cartilage thickness varied significantly among compartment and subcompartment, being highest in the patella, followed by LT, LFC, MFC, and MT ($p < 0.001$)(Table 4). After adjustment for baseline $T_{1\rho}$, the estimated mean cartilage thickness increased significantly during follow-up in patients ($p = 0.027$).

Post-hoc analysis showed that ACL-injured patients displayed significant cartilage thickening in MFC 3 ($p = 0.029$), and significant cartilage thinning in LT 3 ($p = 0.006$) compared to controls at baseline. At the 2-year follow-up, the cartilage in MFC 3 ($p = 0.002$) and MFC 4 ($p = 0.01$) of ACL-injured knees were both significantly thicker than the cartilage in controls. In addition, cartilage in LT 3 thickened with respect to the cartilage at baseline, but remained significantly thinner than the cartilage in controls ($p = 0.05$).

### $T_{1\rho}$ and $T_2$ Quantification of Cartilage

The estimated mean relaxation times were significantly higher in patients than controls, whether assessed via $T_{1\rho}$ ($p = 0.026$) or $T_2$ ($p = 0.013$). Significant changes during the two-year follow-up were identified by both $T_{1\rho}$ ($p = 0.004$) and $T_2$ ($p = 0.02$). Interestingly for $T_{1\rho}$ measurements there was a significant interaction between side and year ($p < 0.001$), with $T_{1\rho}$ increasing in the medial side and decreasing in the lateral side during follow-up; while no significant interaction between side and year was detected for $T_2$ ($p = 0.2$), Table 5. Neither $T_{1\rho}$ nor $T_2$ values varied significantly between sides but both varied significantly among bones, among compartments, and between layers (all $p < 0.001$), Table 5.

Models of $T_{1\rho}$ and $T_2$ levels stratified by bone, side, and layer showed the effect of ACL injury on cartilage was more pronounced in some locations than others - a finding which was further explored in post-hoc analyses. According to both $T_{1\rho}$ and $T_2$, injury effects at baseline and over time were very strong in the superficial cartilage of the LT ($T_{1\rho}$: Group $p = 0.05$, Year $p = 0.06$; $T_2$: Group $p = 0.008$, Year $p = 0.015$)(Table 6(b) and (e)). At this location, the effect was strongest at baseline and appeared to resolve over time. The $T_{1\rho}$ of deep cartilage of the LFC showed a similar strong initial effect that resolved over time (Table 6(a)), but according to $T_2$ these effects were not as strong and appeared to persist (Table 6(d)). Finally, the relaxation times appeared to increase over time in the superficial cartilage of the MFC; however, this was statistically significant for $T_{1\rho}$ (Year $p = 0.022$) (Table 6(a)) and not $T_2$.

Post-hoc analysis showed that at baseline, the $T_{1\rho}$ values of LT 3 and MFC 4 were significantly elevated compared with that of the control subjects (LT 3: 42.9 (6.2) ms vs 36.9 (2.6) ms, p = 0.001; MFC 4: 39.2 (6.9) ms vs 34.3 (4.7) ms, p = 0.018). Significance was also observed in the $T_2$ of LT 3 (32.5 (4.8) ms vs 28.3 (3.2) ms, p = 0.01) and MFC 2 (31.5 (2.4) ms vs 29.1 (2.7) ms, p = 0.041) between patients and controls.

At 1-year, $T_{1\rho}$ in LT 3 decreased but increased in MFC 4. Both values continued to be significantly higher than knees of control subjects (LT 3: 39.5 (3.6) ms, p = 0.033; MFC 4: 39.1 (4.5) ms, p = 0.004). In addition, $T_{1\rho}$ values in MFC 2 (p = 0.011), MFC 3 (p = 0.006), and MT 2 (p = 0.001) of ACL-injured knees were significantly higher than controls. $T_2$ of LT 3 (p = 0.011) in patients was also significantly greater than that of controls.

At 2-year, $T_{1\rho}$ in LT 3 increased compared with that at 1-year, and stayed significantly higher than controls (41.2 (5.3) ms, p = 0.012). $T_{1\rho}$ values in MFC 2 (p = 0.016), MFC 3 (p = 0.011), and MFC 5 (p = 0.011) of ACL-injured knees were also significantly greater than control values.

Laminar analysis showed $T_{1\rho}$ values in the LT 3 superficial layer were significantly higher than controls at baseline (p = 0.004), but decreased at 1-year and 2-year. In the deep layer of LT 3, $T_{1\rho}$ values at baseline and 1-year were not significantly different from the control values; but became significantly elevated compared to controls at 2-year (p = 0.014). $T_2$ in LT 3 was very similar to that of $T_{1\rho}$ (Figure 1).

At 1-year follow-up, $T_{1\rho}$ values in the superficial layer of MFC 2 (p = 0.009), MFC 3 (p = 0.001), and MT 2 (p = 0.002) were significantly elevated compared to that of control knees. $T_{1\rho}$ values continued to increase in the superficial layer of MFC 2 (p = 0.01), MFC 3 (p = 0.002), and MT 2 (p = 0.01) at 2-year. Only the $T_2$ value of MFC 3 superficial layer increased significantly over the two-year period (p = 0.05). The $T_2$ value of MFC 3 deep layer was also significantly elevated compared to controls at 1-year (p = 0.04).

In both groups, $T_{1\rho}$ and $T_2$ in MFC 3 at baseline were correlated with MFC 4. At 1-year and 2-year, $T_{1\rho}$ in MFC 3 remained highly correlated with MFC 4, and became significantly correlated with MT 2 ($p < 0.05$).

### Relationship between $T_{1\rho}$ Progression and Baseline Meniscal Damage and BMEL

No significant effect of meniscal injury, BMEL volume at baseline, or demographic characteristics (age, sex, BMI) on $T_{1\rho}$ and $T_2$ progression was observed. Post-hoc analysis showed that patients with meniscal lesions at baseline had significantly higher $T_{1\rho}$ values in MFC 3, MFC 4, and MT 2 and significantly higher $T_2$ values in MFC 3 at 2-year follow-up compared to controls ($p < 0.05$), while no significant difference in $T_{1\rho}$ and $T_2$ values was observed between patients without meniscal lesions and controls (Table 7).

## Discussion

In this study, quantitative MRI techniques at 3 T were employed to characterize the cartilage matrix and morphology of ACL-injured knees two years after surgical reconstruction. Significantly elevated $T_{1\rho}$ and $T_2$ values were observed at baseline and during follow up in ACL-injured knees compared to controls, and significant changes were also found in cartilage thickness of patients compared to controls.

At baseline, $T_{1\rho}$ and $T_2$ measurements in the posterolateral tibia (LT 3) was significantly elevated compared with values in control knees. In addition, cartilage lesions were identified in LT 3 of 9 ACL-injured patients (60.0%), while BMELs were found in the lateral tibia of

14 ACL-injured patients (93.3%). The high prevalence of BMEL in LT was consistent with previous reports[30–32]. The elevation of $T_{1\rho}$ values in regions overlying BMELs are consistent with our previous cross-sectional studies[10, 27]. These results suggest that lateral tibia, especially LT 3, had the most severe damage during acute ACL injury and $T_{1\rho}$ and $T_2$ can detect the early changes within the cartilage matrix initiated at the time of injury.

A significant interaction between the side and year dependency of $T_{1\rho}$ values was evident among ACL-injured patients. $T_{1\rho}$ values increased in the medial compartments and decreased in the lateral compartments over the two-year study, suggesting early degeneration in the medial side and partial recovery in the lateral side. At 1-year follow-up, $T_{1\rho}$ values in LT 3 decreased significantly from the baseline measurement, but remained significantly elevated compared with $T_{1\rho}$ values in control subjects. This result implies that despite the complete resolution of seven of the BMELs (50%) in the lateral tibia, the cartilage overlying these BMELs may not be fully repaired. Interestingly, at the 2-year follow-up, $T_{1\rho}$ values in LT 3 increased from its 1-year measurement, and remained significantly elevated compared with $T_{1\rho}$ values in controls. This may be due to the increased loss of proteoglycans associated with the progressive degenerative processes seen in early stages of OA. This potential partial recovery and early degeneration in the lateral side needs to be confirmed in future studies with a larger cohort and a longer follow up.

Furthermore, laminar analysis of the posterolateral tibia at baseline revealed that $T_{1\rho}$ values in the superficial layer decreased from baseline to two-year follow-up, while $T_{1\rho}$ in the deep layer increased over the two year period. The initial increase in $T_{1\rho}$ in the superficial layer may be due to local loss of proteoglycans caused by the initial injury and is compensated for by recovery mechanisms two years after injury. The observed $T_{1\rho}$ elevation in the deep layer of LT 3 two years after injury indicated potential cartilage degeneration and suggested different biochemical responses and recovery mechanisms in the two layers.

In the medial side, there was a general increase in the $T_{1\rho}$ values of the tibiofemoral cartilage in ACL-injured knees. In particular, $T_{1\rho}$ values of weight-bearing and cartilage-on-cartilage regions of the femoral condyle showed the most significant increase from baseline to the two-year follow-up when compared to values of control knees. Moreover, strong correlations between the $T_{1\rho}$ elevation in the weight-bearing regions of the tibiofemoral cartilage of ACL-injured patients at the 1-year and 2-year follow-up were observed. Previous kinematic studies of ACL-reconstructed knees have reported substantially altered tibiofemoral motion, resulting in a shift of which regions of cartilage are in contact[33–35]. These results suggest abnormal joint kinematics in the medial side of ACL-injured knees may cause articular cartilage damage and the initiation of the early stages of OA. Laminar analysis of the weight bearing tibiofemoral cartilage showed that $T_{1\rho}$ of the superficial layers were significantly elevated compared with values of control knees at the 1-year and 2-year follow-up. These results are consistent with a previous study that reported surface changes including damage and loss of proteoglycans in load-bearing regions of ACL-injured knees[35]. As shown in Figure 1, the site of early degeneration in LT 3 and MFC 3 at 2-year is different, with damage originating in the deep layer of LT 3 and the superficial layer of MFC 3. This implies that ACL injury may induce different degenerative mechanisms in these cartilage regions.

In this study, one patient had KL = 2, indicating moderate OA. At baseline, this patient had greater $T_{1\rho}$ in all subcompartments than the other patients except for LT 3. No significant difference was observed for $T_2$. This patient had a higher rate of $T_{1\rho}$ increase from baseline to 2-year in all subcompartments of the LT and MT than the mean $T_{1\rho}$ increase from other patients. Not much difference was observed in the LFC or MFC. This observation suggested

that a higher baseline degree of OA may cause a higher rate of cartilage degradation after ACL injury, which warrants further investigations with larger cohorts.

Significant spatial variation of cartilage morphology was also observed among subcompartments. In the posterolateral tibia of ACL-reconstructed knees at baseline, cartilage was significantly thinner than the cartilage of control knees. Previous studies have also reported similar findings that the lateral tibia of reconstructed knees showed cartilage thinning, albeit the difference was not significant[30, 36]. The increased thickness and decreased $T_{1\rho}$ values in the posterolateral tibia during follow up of the patients suggest partial recovery of cartilage in these regions.

In the medial side, cartilage was significantly thicker in weight-bearing regions of the femoral condyle in ACL-injured knees compared with control knees over the two years. As previously reported, the thickest areas of cartilage occur where cartilage-on-cartilage contact was present, and most likely develop as a response to loading[37]. Cartilage swelling in the medial tibiofemoral compartment has also been reported in patients with minimal severity of radiographic OA[38]. In conjunction with increased $T_{1\rho}$ values of the weight-bearing medial tibiofemoral cartilage, these results suggest early degeneration in these regions with increase of water content, decrease of proteoglycan, and cartilage swelling.

Previous studies have demonstrated strong association among meniscal injury, BMEL volume, and cartilage degeneration[39–41]. The current study was unable to identify meniscal injury and baseline measurement of BMEL volume as risk factors for elevated $T_{1\rho}$ or $T_2$ in cartilage. This may be due to the small sample size and larger cohorts are required to increase the statistical power. However, post-hoc analysis indicated that ACL-injured patients with lesions in the posterior horns of the medial meniscus had significantly higher $T_{1\rho}$ values in weight-bearing regions of the tibiofemoral cartilage than that of controls over the two year period, whereas patients without medial meniscal tears did not. Interestingly, only the cartilage-on-cartilage regions of the medial tibia exhibited an increase in $T_{1\rho}$ values from baseline to two-year follow-up. In addition, five patients (33%) had BMEL in the MFC at baseline. The prevalence of BMEL in the MFC may be due to traumatic chondral shear. All five patients all had cartilage lesions (with scores of 2 or higher) in this region and no lesions in the medial meniscus. Three patients also developed new bone marrow lesions in the lateral or the medial aspect of the femur at 1-year, and one patient developed a new lesion in the lateral femur after two years. Of the new BMELs that developed at 1-year, all became resolved by the 2-year follow-up, indicating transient bone remodeling.

The findings of this study were consistent with our previous 1-year study. The previous study's cohort was small and may have lacked the statistical power to reveal significance in the $T_2$ of several layers. Nevertheless, large scale studies are needed to confirm the findings of the current study and to correlate different types of meniscal tears to cartilage injury at baseline and longitudinal follow-up. Another limitation of the present report was that data from uninjured contralateral knees in patients with ACL injuries were not available. The current study also lacks longitudinal data in controls. However in unpublished data from our lab, a control group with a similar age and BMI range ($38.8 \pm 11.1$ years, $24.0 \pm 3.4$ kg/m$^2$) did not show significant differences between baseline $T_{1\rho}$ ($p > 0.27$) , $T_2$, ($p > 0.33$) and thickness ($p > 0.24$) values in compartments and those at 2-year.

In conclusion, $T_{1\rho}$ and $T_2$ quantifications revealed persistent damage in the posterolateral tibial cartilage and progressive degeneration in the central regions of the medial tibiofemoral cartilage in ACL-injured knees two years after reconstruction. This study also found that cartilage thinning occurs in the posterolateral tibia after an acute ACL injury, while cartilage thickening occurs in the central medial aspect of the femur. Quantitative MRI provides

powerful *in vivo* tools to quantitatively evaluate early changes of cartilage matrix and morphology after acute ACL injury and reconstruction. Such quantitative tools will help stratify injury, monitor and potentially predict post-traumatic OA development in acutely injured joints.

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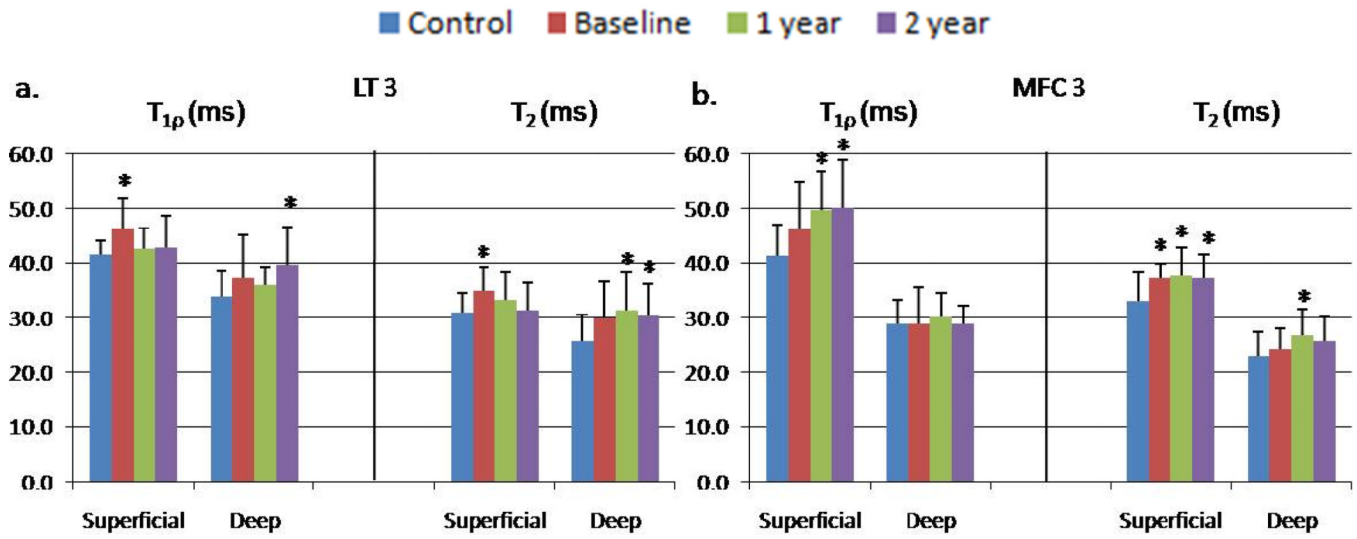


**Figure 1.**

$T_{1\rho}$ and $T_2$ values in superficial and deep layers of cartilage in (a) LT 3 and (b) MFC 3. *The difference between controls and ACL-injured knees at the given time point was statistically significant ($p < 0.05$).

**Table 1**

Sagittal Imaging Protocol at 3.0 T

| Imaging Parameters | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Sequence** | **TR/TE* (ms)** | **FOV (cm)** | **Matrix size** | **Slice Thickness** | **Flip Angle** | **VPS** | **Other Parameters** |
| $T_2$-weighted fat saturated FSE | 4300/51 | 14 | 512 × 256 | 2.5 mm | - | - | - |
| 3D fat-suppressed High-resolution SPGR | 15/6.7 | 14 | 512 × 512 | 1 cm | 12° | - | - |
| 3D $T_{1\rho}$ | 9.3/3.7 | 14 | 256 × 192 | 4 mm | - | 64 | TSL (ms): 0, 10, 40 80 FSL (Hz): 500 |
| 3D $T_2$ | 9.3/3.7 | 14 | 256 × 192 | 4 mm | - | 64 | Preparation TE (ms): 2.9, 13.6, 24.3, 45.6 |

*TR/TE: repetition time/echo time; FOV: field of view; VPS: view per segment; TSL: time of spin lock; FSL: frequency of spin lock.

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**Table 2**

Modified Subscores of the Whole-Organ Magnetic Resonance Imaging Score System

| Articular Features | Grade |
|---|---|
| Meniscal lesion | 0 = normal meniscus, 1 = signal abnormality, 2 = vertical tear, 3 = horizontal tear, 4 = complex tear with both horizontal and vertical components, 5 = maceration of the meniscus |
| Effusion | 0 = normal, 1 = mild, 2 = moderate, 3 = severe |
| Cartilage Lesion | Unmodified 8-point scale[26] |

**Table 3(a)**

Baseline characteristics of study participants by gender and injury status. Mean (Min -Max).

| | Women | | Men | | All | | |
|---|---|---|---|---|---|---|---|
| | **Healthy (n=8)** | **Injured (n=8)** | **Healthy (n=8)** | **Injured (n=7)** | **Healthy (n=16)** | **Injured (n=15)** | **2-sided KW test†** |
| Age (years) | 29.4 (24 – 38) | 33.6 (23 – 49) | 36.3 (23 – 57) | 36.9 (30 – 45) | 32.8 (23 – 57) | 35.1 (23 – 49) | p = 0.15 |
| BMI (kg/m$^2$) | 22.9 (20 – 29)* | 22.4 (19 – 25) | 25.9 (22 – 29) | 24.3 (21 – 27) | 24.4 (20 – 29) | 23.3 (19 – 27) | p = 0.44 |
| Injury to Baseline MRI(days) | - | 37.3 (8 – 56) | - | 56.3 (15 – 147) | - | 46.1 (8 – 147) | - |
| MRI to Surgery (days) | - | 36.6 (9 – 98) | - | 37.3 (1 – 92) | - | 36.9 (1 – 98) | - |
| Injury to Surgery (days) | - | 73.9 (41 – 114) | - | 93.6 (31 – 152) | - | 83.1 (31 – 152) | - |

*One value missing

†Compares healthy and injured participants without adjusting for gender. KW=Kruskal-Wallis.

**Table 3(b)**

Baseline clinical characteristics of injured participants by gender: counts of categorical variables. Mean (Min - Max).

| | Women (n = 8) | Men (n = 7) | All (n = 15) |
|---|---|---|---|
| KL Scores | | | |
| 0 | 6 | 6 | 12 |
| 1 | 1 | 1 | 2 |
| 2 | 1 | 0 | 1 |
| Effusion | | | |
| 0 | 0 | 0 | 0 |
| 1 | 3 | 2 | 5 |
| 2 | 4 | 5 | 9 |
| 3 | 1 | 0 | 1 |
| Cartilage Lesion | | | |
| Patella | 3 | 3 | 6 |
| MFC | 1 | 3 | 4 |
| LFC | 2 | 0 | 2 |
| MT | 0 | 0 | 0 |
| LT | 5 | 4 | 9 |
| Max | 2.1 (0 – 5) | 2.3(0 – 5) | 2.2 (0 – 5) |
| Total | 3.1 (0 – 7) | 3.4 (0 – 8) | 3.3 (0 – 8) |
| Graft Type | | | |
| Hamstring | 4 | 4 | 8 |
| Allograft | 4 | 3 | 7 |
| Medial Meniscal Lesion | | | |
| 0 | 4 | 4 | 8 |
| 1 | 2 | 2 | 4 |
| 2 | 0 | 1 | 1 |
| 3 | 0 | 0 | 0 |
| 4 | 1 | 0 | 1 |
| 5 | 1 | 0 | 1 |
| Lateral Meniscal Lesion * | | | |
| 0 | 6 | 2 | 8 |
| 1 | 0 | 0 | 0 |
| 2 | 0 | 1 | 1 |
| 3 | 1 | 0 | 1 |
| 4 | 0 | 3 | 3 |
| 5 | 1 | 1 | 2 |

[*] One patient showed a root tear in the lateral posterior horn.

**Table 4**

Adjusted mean cartilage thickness in defined compartments. Mean (SD).

| Bone | Side | Controls | Patients | | |
|---|---|---|---|---|---|
| | | | Year 0 | Year 1 | Year 2 |
| Femur | | | | | |
| | Medial | 1.06 (0.21) | 1.13 (0.26) | 1.13 (0.27) | 1.19 (0.30) |
| | Lateral | 1.15 (0.30) | 1.22 (0.30) | 1.22 (0.26) | 1.28 (0.32) |
| Tibia | | | | | |
| | Medial | 0.82 (0.23) | 0.89 (0.18) | 0.89 (0.21) | 0.95 (0.18) |
| | Lateral | 1.36 (0.49) | 1.44 (0.47) | 1.43 (0.49) | 1.49 (0.45) |
| Patella | | 2.04 (0.36) | 2.11 (0.43) | 2.11 (0.52) | 2.17 (0.63) |

**Table 5**

$T_{1\rho}$ and $T_2$ tests for fixed effects.

| | $T_{1\rho}$ (1816 Obs) | | | $T_2$ (1720 Obs) | | |
|---|---|---|---|---|---|---|
| **Effect** | **Num DF** | **F Value** | **Pr > F** | **Num DF** | **F Value** | **Pr > F** |
| Group | 1 | 4.99 | 0.0256 | 1 | 6.19 | 0.0130 |
| Year | 2 | 5.50 | 0.0042 | 2 | 3.89 | 0.0205 |
| Cpmt | 4 | 23.45 | <.0001 | 4 | 61.76 | <.0001 |
| Group * Cpmt | 5 | 1.36 | 0.2367 | 5 | 0.94 | 0.4520 |
| Year * Cpmt | 8 | 1.66 | 0.1041 | 8 | 3.58 | 0.0004 |
| Side | 1 | 0.08 | 0.7810 | 1 | 1.78 | 0.1821 |
| Side * Year | 2 | 9.97 | <.0001 | 2 | 1.68 | 0.1859 |
| Side * Cpmt | 3 | 21.25 | <.0001 | 3 | 36.01 | <.0001 |
| Layer | 1 | 458.31 | <.0001 | 1 | 175.20 | <.0001 |
| Layer * Year | 2 | 1.12 | 0.3255 | 2 | 1.43 | 0.2394 |
| Layer * Cpmt | 4 | 55.34 | <.0001 | 4 | 60.10 | <.0001 |
| Bone | 1 | 69.75 | <.0001 | 1 | 149.94 | <.0001 |
| Bone * Year | 2 | 1.35 | 0.2601 | 2 | 0.07 | 0.9363 |
| Bone * Cpmt | 2 | 13.05 | <.0001 | 2 | 8.67 | 0.0002 |
| Side * Bone | 1 | 14.06 | 0.0002 | 1 | 19.18 | <.0001 |
| Layer * Bone | 1 | 19.01 | <.0001 | 1 | 8.22 | 0.0042 |

Cmpt: Subcompartment

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**Table 6(a)**

Mean $T_{1\rho}$ (ms) in femur.

| **Medial** | **Superficial** | | | | **Deep** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Controls** | **Patients** | | | **Controls** | **Patients** | | |
| **Subcompartment** | | **Year 0** | **Year 1** | **Year 2** | | **Year 0** | **Year 1** | **Year 2** |
| **2** | 39.1 | 39.7 | **43.9** | **44.3** | 33.3 | 35.1 | 36.1 | 36.6 |
| **3** | 41.4 | 46.1 | **49.8** | **50.3** | 29.0 | 28.8 | 30.2 | 28.8 |
| 4 | 39.4 | 41.3 | 44.0 | 43.7 | 31.0 | 34.2 | 33.5 | 30.9 |
| 5 | 40.7 | 43.5 | 42.3 | 42.4 | 36.9 | 39.1 | 39.0 | 41.2 |
| Mean (SE) | 40.2 (1.07) | 42.7 (1.13) | 45.0 (1.11) | 45.5 (1.18) | 32.5 (0.86) | 34.5 (0.91) | 34.7 (0.89) | 34.6 (0.97) |
| Mean Difference * (95% CI) | -- | 2.55 (−0.54, 5.64) | 4.83 (1.77, 7.89) | 5.33 (2.16, 8.49) | -- | 1.97 (−0.51, 4.46) | 2.13 (−0.33, 4.58) | 2.09 (−0.48, 4.66) |
| | Group p = 0.10, **Year p = 0.022** † | | | | Group p = 0.12, Year p = 0.99 | | | |
| Lateral | Superficial | | | | Deep | | | |
| | Controls | Patients | | | Controls | Patients | | |
| Subcompartment | | Year 0 | Year 1 | Year 2 | | Year 0 | Year 1 | Year 2 |
| 1 | 46.7 | 46.4 | 44.0 | 48.6 | 37.8 | 39.3 | 37.1 | 38.7 |
| 2 | 37.1 | 38.4 | 37.0 | 37.3 | 28.8 | 30.4 | 27.8 | 27.7 |
| 3 | 43.6 | 44.1 | 44.8 | 43.0 | 32.8 | 34.3 | 31.7 | 31.4 |
| 4 | 43.2 | 43.3 | 43.9 | 44.6 | 36.0 | 37.9 | 35.7 | 35.1 |
| 5 | 40.0 | 45.6 | 42.6 | 43.9 | 36.5 | 39.7 | 37.8 | 39.2 |
| Mean (SE) | 42.1 (0.87) | 43.9 (0.91) | 42.4 (0.89) | 43.7 (0.94) | 34.4 (0.73) | 36.5 (0.76) | 34.0 (0.75) | 34.5 (0.79) |
| Mean Difference (95% CI) | -- | 1.76 (−0.73, 4.26) | 0.31 (−2.17, 2.78) | 1.54 (−1.00, 4.08) | -- | 2.09 (0.01, 4.18) | −0.35 (−2.42, 1.71) | 0.083 (−2.05, 2.22) |
| | Group p = 0.16, Year p = 0.08 | | | | **Group p = 0.049, Year p = 0.001** | | | |

For all subtables in Table 6:

* Differences are relative to healthy controls.

† Group effect compares patients with controls at Year 0. Among patients, Year effect compares Years 1 and 2 with Year 0.

The values highlighted with red are those with significant difference compared to controls during post-hoc analysis.

**Table 6(b)**

Mean $T_{1\rho}$ (ms) in tibia.

| **Medial** | **Superficial** | | | | **Deep** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Controls** | **Patients** | | | **Controls** | **Patients** | | |
| **Subcompartment** | | **Year 0** | **Year 1** | **Year 2** | | **Year 0** | **Year 1** | **Year 2** |
| 1 | 30.9 | 32.7 | 31.6 | 31.3 | 32.2 | 31.8 | 33.8 | 33.8 |
| **2** | 37.5 | 39.9 | **44.1** | **47.3** | 26.4 | 24.1 | 26.4 | 28.6 |
| 3 | 37.9 | 35.7 | 37.3 | 37.6 | 31.5 | 32.2 | 32.6 | 35.9 |
| Mean (SE) | 35.6 (1.33) | 36.7 (1.39) | 37.7 (1.36) | 38.8 (1.46) | 30.0 (1.31) | 30.2 (1.38) | 30.9 (1.35) | 32.5 (1.47) |
| Mean Difference (95% CI) | -- | 1.10 (−2.73, 4.94) | 2.10 (−1.70, 5.89) | 3.26 (−0.68, 7.19) | -- | 0.18 (−3.61, 3.98) | 0.96 (−2.78, 4.71) | 2.50 (−1.43, 6.42) |
| | Group p = 0.57, Year p = 0.27 | | | | Group p = 0.92, Year p = 0.30 | | | |
| Lateral | Superficial | | | | Deep | | | |
| | Controls | Patients | | | Controls | Patients | | |
| Subcompartment | | Year 0 | Year 1 | Year 2 | | Year 0 | Year 1 | Year 2 |
| 1 | 36.6 | 40.6 | 36.7 | 34.7 | 30.5 | 30.1 | 31.2 | 32 |
| 2 | 38.5 | 37.1 | 40.4 | 38.9 | 26.1 | 24.5 | 25.4 | 26.6 |
| **3** | 41.5 | **46.3** | 42.6 | 42.8 | 33.9 | 37.4 | 36.1 | **39.6** |
| Mean (SE) | 38.9 (0.88) | 41.4 (0.93) | 39.9 (0.91) | 39.2 (0.98) | 30.2 (1.05) | 31.1 (1.11) | 30.9 (1.09) | 32.4 (1.18) |
| Mean Difference (95% CI) | -- | 2.49 (−0.06, 5.04) | 1.02 (−1.50, 3.54) | 0.27 (−2.35, 2.89) | -- | 0.87 (−2.18, 3.93) | 0.74 (−2.27, 3.76) | 2.23 (−0.92, 5.37) |
| | **Group p = 0.05, Year p = 0.06** | | | | Group p = 0.57, Year p = 0.42 | | | |

**Table 6(c)**

Mean $T_{1\rho}$ (ms) in patella.

| | Superficial | | | | Deep | | | |
|---|---|---|---|---|---|---|---|---|
| | Controls | Patients | | | Controls | Patients | | |
| | | Year 0 | Year 1 | Year 2 | | Year 0 | Year 1 | Year 2 |
| Mean (SE) | 43.9 (1.53) | 46.5 (1.62) | 43.5 (1.58) | 45.6 (1.73) | 33.0 (1.44) | 36.0 (1.52) | 32.0 (1.49) | 34.3 (1.61) |
| Mean Difference (95% CI) | -- | 2.58 (−2.02, 7.18) | −0.39 (−4.93, 4.14) | 1.71 (−3.05, 6.47) | -- | 2.99 (−1.33, 7.32) | −1.03 (−5.29, 3.24) | 1.31 (−3.15, 5.77) |
| | Group p = 0.26, Year p = 0.25 | | | | Group p = 0.17, Year p = 0.055 | | | |

**Table 6(d)**

Mean $T_2$ (ms) in femur.

| **Medial** | **Superficial** | | | | **Deep** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Controls** | **Patients** | | | **Controls** | **Patients** | | |
| **Subcompartment** | | **Year 0** | **Year 1** | **Year 2** | | **Year 0** | **Year 1** | **Year 2** |
| 2 | 30.1 | 30.7 | 30.5 | 32.2 | 26.8 | 31.2 | 28.8 | 28.7 |
| **3** | 33.1 | **37.3** | **37.8** | **37.3** | 22.8 | 24.2 | **26.7** | 25.7 |
| 4 | 31.8 | 31.7 | 33.3 | 32.5 | 26.5 | 29.0 | 28.6 | 28.6 |
| 5 | 31.1 | 32.7 | 32.1 | 33.9 | 32.1 | 33 | 33.2 | 35.2 |
| Mean (SE) | 31.5 (0.73) | 33.2 (0.79) | 33.4 (0.72) | 34.1 (0.78) | 27.1 (0.83) | 29.5 (0.89) | 29.3 (0.83) | 29.6 (0.89) |
| Mean Difference (95% CI) | -- | 1.72 (−0.41, 3.85) | 1.89 (−0.16, 3.93) | 2.57 (0.44, 4.69) | -- | 2.42 (0.0, 4.83) | 2.24 (−0.08, 4.57) | 2.50 (0.09, 4.91) |
| | Group p = 0.11, Year p = 0.54 | | | | **Group p = 0.049**, Year p = 0.95 | | | |
| Lateral | Superficial | | | | Deep | | | |
| | Controls | Patients | | | Controls | Patients | | |
| Subcompartment | | Year 0 | Year 1 | Year 2 | | Year 0 | Year 1 | Year 2 |
| 1 | 35.1 | 34.3 | 35.8 | 38.7 | 30.1 | 32.4 | 32.2 | 37.1 |
| 2 | 27.4 | 28.0 | 26.9 | 25.5 | 20.0 | 22.2 | 20.7 | 20.6 |
| 3 | 34.4 | 33.1 | 34.0 | 33.2 | 25.3 | 26.6 | 25.0 | 26.7 |
| 4 | 33.8 | 33.9 | 33.6 | 32.8 | 29.6 | 30.1 | 31.2 | 30.2 |
| 5 | 29.6 | 33.2 | 33.0 | 35.8 | 30.1 | 31.5 | 32.5 | 34.8 |
| Mean (SE) | 32.0 (0.77) | 33.1 (0.81) | 32.6 (0.76) | 33.2 (0.80) | 27.1 (0.79) | 28.8 (0.82) | 28.3 (0.77) | 29.8 (0.81) |
| Mean Difference (95% CI) | -- | 1.00 (−1.21, 3.21) | 0.59 (−1.56, 2.75) | 1,19 (−1.02, 3.40) | -- | 1.69 (−0.56, 3.93) | 1.24 (−0.95, 3.42) | 2.67 (0.43, 4.92) |
| | Group p = 0.37, Year p = 0.63 | | | | Group p = 0.14, Year p = 0.09 | | | |

**Table 6(e)**

Mean $T_2$ (ms) in tibia.

| **Medial** | **Superficial** | | | | **Deep** | | | |
|---|---|---|---|---|---|---|---|---|
| | **Controls** | **Patients** | | | **Controls** | **Patients** | | |
| **Subcompartment** | | **Year 0** | **Year 1** | **Year 2** | | **Year 0** | **Year 1** | **Year 2** |
| 1 | 21.1 | 23.5 | 23.5 | 23.7 | 24.2 | 25.1 | 25.3 | 25.8 |
| 2 | 31.2 | 32.4 | 32.3 | 32.9 | 22.1 | 20.0 | 20.3 | 22.7 |
| 3 | 27.9 | 27.0 | 27.7 | 27.3 | 24.7 | 25.9 | 25.0 | 26.9 |
| Mean (SE) | 26.9 (0.89) | 28.2 (0.93) | 27.8 (0.88) | 28.0 (0.94) | 23.6 (1.37) | 24.5 (1.40) | 23.5 (1.36) | 24.8 (1.41) |
| Mean Difference (95% CI) | -- | 1.36 (−1.22, 3.93) | 0.95 (−1.56, 3.46) | 1.14 (−1.44, 3.72) | -- | 0.89 (−3.01, 4.81) | 0.00 (−3.85, 3.85) | 1.18 (−2.73, 5.10) |
| | Group p = 0.30, Year p = 0.86 | | | | Group p = 0.65, Year p = 0.33 | | | |
| Lateral | Superficial | | | | Deep | | | |
| | Controls | Patients | | | Controls | Patients | | |
| Subcompartment | | Year 0 | Year 1 | Year 2 | | Year 0 | Year 1 | Year 2 |
| 1 | 23.7 | 29.0 | 26.2 | 24.3 | 22.9 | 22.8 | 21.7 | 21.5 |
| 2 | 28.2 | 27.1 | 30.3 | 27.4 | 19.5 | 18.1 | 20.6 | 20.8 |
| **3** | 30.8 | **34.9** | 33.2 | 31.4 | 25.6 | 29.9 | **31.5** | **30.4** |
| Mean (SE) | 27.6 (0.81) | 30.8 (0.87) | 30.0 (0.80) | 28.4 (0.87) | 22.6 (1.06) | 23.7 (1.12) | 24.6 (1.07) | 24.6 (1.10) |
| Mean Difference (95% CI) | -- | 3.24 (0.86, 5.62) | 2.39 (0.09, 4.69) | 0.81 (−1.57, 3.19) | -- | 1.09 (−2.01, 4.18) | 1.95 (−1.07, 4.96) | 1.96 (−1.13, 5.05) |
| | **Group p = 0.008, Year p = 0.015** | | | | Group p = 0.49, Year p = 0.55 | | | |

**Table 6(f)**

Mean $T_2$ (ms) in patella.

| | Superficial | | | | Deep | | | |
|---|---|---|---|---|---|---|---|---|
| | Controls | Patients | | | Controls | Patients | | |
| | | Year 0 | Year 1 | Year 2 | | Year 0 | Year 1 | Year 2 |
| Mean (SE) | 33.2 (0.99) | 35.7 (1.09) | 35.3 (1.00) | 36.1 (1.09) | 26.5 (0.89) | 26.9 (0.97) | 28.7 (0.88) | 29.4 (0.97) |
| Mean Difference (95% CI) | -- | 2.55 (−0.51, 5.62) | 2.15 (−0.78, 5.07) | 2.86 (−0.21, 5.93) | -- | 0.42 (−2.31, 3.15) | 2.24 (−0.35, 4.84) | 2.85 (0.12, 5.58) |
| | Group p = 0.10, Year p = 0.83 | | | | Group p = 0.75, Year p = 0.11 | | | |

**Table 7**

$T_{1\rho}$ and $T_2$ data for cartilage in ACL-injured patients with (+) and without (−) meniscal tears in the medial posterior horn. Mean (SD).

| | | Baseline | | 1 year | | 2 year | |
|---|---|---|---|---|---|---|---|
| | | + | − | + | − | + | − |
| $T_{1\rho}$ | MFC 3 | **39.76 (3.4)** | 36.24 (7.6) | **42.00 (3.4)** | 37.27 (5.2) | **40.40 (4.3)** | 38.62 (6.1) |
| | MFC 4 | **42.53 (8.3)** | 36.74 (4.7) | **41.37 (3.1)** | 37.12 (4.8) | **38.18 (3.6)** | 36.43 (8.5) |
| | MT 2 | 30.22 (3.9) | 33.51 (6.3) | **36.72 (2.1)** | 34.75 (4.1) | **39.05 (3.9)** | 35.26 (9.2) |
| | MT 3 | 34.18 (3.5) | 34.90 (4.8) | 35.62 (5.9) | 34.07 (3.5) | 36.26 (2.9) | 32.40 (5.3) |
| $T_2$ | MFC 3 | **30.96 (1.1)** | 29.57 (3.8) | **34.58 (3.2)** | 28.84 (2.9) | **34.07 (3.1)** | 28.93 (2.9) |
| | MFC 4 | 31.35 (3.7) | 29.13 (3.6) | 32.12 (2.7) | 29.21 (3.7) | 32.38 (2.6) | 28.58 (2.8) |
| | MT 2 | 27.22 (5.8) | 26.8 (7.6) | 26.14 (4.8) | 26.87 (4.4) | 27.35 (3.2) | 28.10 (7.2) |
| | MT 3 | 26.59 (4.1) | 27.34 (5.1) | 27.18 (5.0) | 26.21 (4.0) | 29.04 (5.4) | 25.24 (2.4) |

The values highlighted with red are those with significant difference compared to controls during post-hoc analysis.